SMITHKLINE BEECHAM PLC *WO 200241889-A2

2001.06.04 2001-013517(+2000GB-028708) *(2002.05.30)* A61K 31/404, A61P 25/24

Composition useful for the treatment of e.g. depression comprises new and known indole compounds and a carrier (Eng)

C2002-207206 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW)

Addnl. Data: BROMIDGE S M

2001.11.16 2001WO-EP13411, 2001.06.04 2001GB-013517

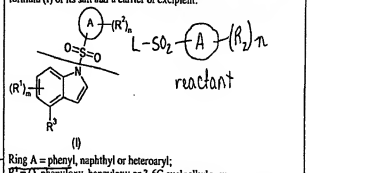
NOVELTY

A composition comprises a new or known indole compound (I) and a carrier or excipient.

B(6-D1, 14-E10, 14-E10C, 14-E11, 14-J1A1, 14-J1A4, 14-J1B, 14-J1B3, 14-J1B4, 14-J7, 14-L6, 14-M1A, 14-M1B, 14-M1C) 5

DETAILED DESCRIPTION

A composition comprises a new or known indole compound of formula (I) or its salt and a carrier or excipient.




(I)

Ring A = phenyl, naphthyl or heteroaryl;

$R^2$ = Q, phenyloxy, benzyloxy or 3-6C cycloalkyloxy;

Q = halo, 1-6C alkyl, 1-6C alkoxy, 1-6C alkanoyl, CN, $CF_3$ or $OCF_3$;

$R^2$ = Q, 3-6C cycloalkyl, 1-6C alkylthio, 1-6C alkylsulfinyl, 1-6C



alkylsulfonyl, $OCH_2CF_3$, OH, hydroxy-1-6C alkyl, hydroxy-1-6C alkoxy, 1-6C alkoxycarbonyl, 1-6C alkoxy-1-6C alkoxy, nitro, amino, N-(1-6C alkyl)$_2$, NH-1-6C alkyl, 1-6C alkylamino, di-1-6C alkylamino, C(O)O$R^4$, CONR$^5$R$^6$, NR$^5$COR$^6$, or phenyl, naphthyl or heteroaryl (all optionally substituted by $R^1$);

$R^4$-$R^6$ = H or 1-6C alkyl; or

$R^5$+$R^6$ = 5-7 membered azacyclic ring optionally containing an additional N, S or O;

$R^3$ = 5-7 membered mono- or bicyclic heterocyclic ring containing 1-3 N, S and/or O and optionally substituted by at least one 1-6C alkyl;

m = 0-4; and

n = 0-5.

INDEPENDENT CLAIMS are also included for:

(1) New compounds (I) and their salts, excluding 4-(1-methyl-4-piperidinyl)-1-(phenylsulfonyl)-1H-indole, 4-(1,3-dithian-2-yl)-1-[4-methylphenyl)sulfonyl]-1H-indole, or 1-[(4-methylphenyl)sulfonyl]-4-(4-morpholinyl)-1H-indole; and

(2) preparation of new compounds (I).

ACTIVITY

Antidepressant; Tranquilizer; Nootropic; Neuroprotective; Neuroleptic; Anticonvulsant; Antimigraine; Antiparkinsonian; Antiaddictive; Anorectic; Antiinflammatory.

MECHANISM OF ACTION

5-$HT_6$ receptor antagonist.

USE

In therapy or in the manufacture of medicament for the treatment of depression, anxiety, cognitive memory disorders, Alzheimer's disease, age-related cognitive decline, mild cognitive impairment, attention deficit disorder/hyperactivity syndrome, and schizophrenia (all claimed). Also useful for the treatment of epilepsy, obsessive compulsive disorders such as anorexia and bulimia, panic attack, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepine disorders associated with spinal trauma and/or injury such as hydrocephalus; and in the treatment of certain gastrointestinal disorder such as irritable bowel syndrome.

SPECIFIC COMPOUNDS

175 Compounds (I) are specifically claimed, e.g. 1-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-4-piperazin-1-yl-1H-indole



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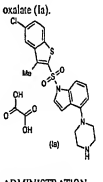
oxalate (Ia).




ADMINISTRATION

Administration of (I) is 0.05-1000 (preferably 0.2-5) mg, more than once (preferably 2-3) times a day orally, parenterally or rectally.

EXAMPLE

To a solution of 4-(4-benzyl-piperazin-1-yl)-1-(5-chloro-3-meihyl-benzo[b]thiophene-2-sulfonyl)-1H-indole (93 mg) in dry 1,2-dichloromethane (5 ml) was added N,N-diisopropylethylamine (0.16 ml) and 1-chloroethyl chloroformate (0.09 ml). The solution was stirred at 80 °C under argon for 50 minutes and then concentrated *in vacuo*. The residue was redissolved in methanol (10 ml) and the solution was refluxed for 1.3 hours. After concentrating the mixture, the residue was redissolved in dichloromethane (15 ml) and the solution was washed. The organic phase was dried, concentrated and chromatographed to give a free base (55 mg) of 1-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-4-piperazin-1-yl-1H-indole (Ia'). Treatment of a solution of (A) in DCM (1 ml) with an oxalic acid solution (1.5 equivalents) in methanol/diethyl ether gave 1-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-4-piperazin-1-yl-1H-indole oxalate (Ia).

DEFINITIONS

Preferred Definitions:

$R^2$ = unsubstituted piperazine ring;

$R^1$ = 5,7-dichloro;

Ring A = phenyl;

n = 1; and
$R^2$ = Cl.

TECHNOLOGY FOCUS

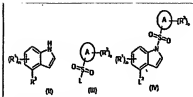
Organic Chemistry - Preparation: Preparation of new compounds (I) comprises:

(1) coupling a compound of formula (II) or its protected derivative with a compound of formula (III) or its protected derivative; removing any protecting groups; and forming a salt;

(2) preparing (I; $R^2$ = optionally substituted piperazinyl or 1,4-diazepanyl group linked to the indole moiety *via* N) by reacting a compound of formula (IV) or its protected derivative with a compound of formula $R^{10}$-H and optionally removing any protecting group and forming a salt;

(3) deprotecting protected compounds (I); or

(4) interconversion of (II) to its salt or derivatives.



(II) (III) (IV)

L = leaving group;

$L^2$ = leaving group (preferably halo, trifluoromethylsulfonyloxy or nonafluorobutylsulfonyloxy); and

$R^{10}$ = optionally protected and/or substituted piperazinyl or 1,4-diazepanyl group.

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